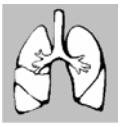
CDHS/CTCA JOINT GUIDELINES
Targeted Skin Testing and Treatment of Latent Tuberculosis Infection in Adults and Children



The following guidelines have been developed by the California Department of Health Services, Tuberculosis Control Branch in consultation with the Executive Committee of the California Tuberculosis Controllers Association. These guidelines are official State recommendations and have been endorsed by the California Tuberculosis Controllers Association.

Recently published guidelines from the American Thoracic Society and Centers for Disease Control and Prevention have recommended a change in nomenclature. The terms "chemoprophylaxis" and "preventive therapy" will no longer be used. Instead, the phrase "treatment of latent tuberculosis infection (LTBI)" is recommended because it more accurately describes the intended intervention. This change in nomenclature will hopefully promote greater understanding of the concept for both patients and providers, resulting in more widespread use of this important tuberculosis (TB) control strategy.

Targeted TB Skin Testing

Targeted tuberculin skin testing for LTBI aims to identify individuals at high risk for TB who would benefit from treatment of LTBI. Skin testing low risk populations will result in unnecessary testing and treatment because of false-positive test results.

High risk can be defined as:

(1) Recent infection with *Mycobacterium tuberculosis*,
(2) The presence of clinical conditions that are associated with an increased risk of progression of LTBI to active TB (see **Appendix 1: Tables 1 and 2**) or
(3) Increased morbidity if progression to TB disease occurs.

Definition of a positive tuberculin skin test

Previous vaccination with BCG is not a contraindication to tuberculin skin testing. Because most persons who have received prior BCG vaccination are from high prevalence areas of the world, previous vaccination should be ignored when interpreting a tuberculin skin test.

I. $\geq$ 5 mm of induration*

A. Persons known or suspected to have HIV infection.

B. Recent contacts to an active case of pulmonary or laryngeal TB.

C. Persons with an abnormal chest radiograph consistent with TB disease.

D. Immunosuppressed individuals (See page 4 **Indications for Treatment of LTBI -TB2 and TB4**, VI-E)

***Note:** The California Department of Corrections considers all inmates high risk, and therefore treats for latent infection all inmates with TST of ≥ 5mm.

II. ≥ 10 mm of induration

All persons except those in I (A) above

Note: The CDC recommends using a 15 mm cutoff for low risk reactors. However, in California, public health departments do not recognize this cutoff because California is a high incidence state and the prevalence of nontuberculous mycobacterial infections is lower than other regions of the United States.

III. Tuberculin skin test conversion

TST conversion is defined as an increase of at least 10 mm of induration from < 10 mm to ≥ 10 mm within two years from a documented negative to positive TST.

Example: a TST of 4 mm that increases in size to 14 mm or more in induration would be considered a skin test conversion.

In some cases, the exact size (in mm) of the previous tuberculin skin test may not be known. In such cases, skin test conversion is defined as a change from a negative to positive tuberculin skin test within a 2-year period.

Evaluation for TB Disease - Symptom review and chest radiography

I. All persons who have a positive tuberculin skin test should undergo symptom review and have a chest radiograph.

A. If the radiograph is normal and the patient is asymptomatic, treatment of LTBI may be indicated (see **Appendix 2**).

B. If the radiograph is normal but the patient has a clinical presentation consistent with tuberculosis, further work-up is indicated and treatment of LTBI should be delayed until active tuberculosis has been ruled out.

II. Bacteriologic studies should be obtained for all persons with an abnormal chest radiograph consistent with tuberculosis even when the radiographic abnormalities appear stable. If bacteriologic studies are obtained, treatment of LTBI should not be initiated until final culture

results are available.

Definition of persons eligible for treatment of LTBI (TB2 and TB4)

The following classes of persons are eligible for treatment of LTBI if they have not received a prior course of treatment for active TB or LTBI. In some cases, individuals may require another course of therapy. Indications for re-treatment include persons with a new close contact to an infectious case who are < 5 years of age, or have HIV/AIDS or other significant immunosuppression. Providers may also choose to retreat persons with previously treated LTBI or active TB who have had new exposure to a highly infectious TB case where extensive transmission has been documented, circumstances suggest a high probability of transmission, or in high risk settings such as prisons or other congregate facilities.

I. TB2 - Tuberculosis infection, no disease:

Significant reaction to tuberculin skin test, negative bacteriologic studies (if done) and no clinical and/or radiographic evidence of tuberculosis. Patients with isolated calcified granulomas or apical pleural thickening are generally classified as TB 2.

II. TB4 - Tuberculosis, no current disease:

A. History of previous episode(s) of tuberculosis, or

B. Abnormal*, but stable, radiographic findings in a person with a positive tuberculin skin test, negative bacteriologic studies, and no clinical and/or radiographic evidence of current disease.

*Abnormal refers to radiographs with parenchymal abnormalities consistent with TB, except isolated calcified granulomas.

Indications for Treatment of LTBI – TB2 and TB4 (See **Appendix 2**)

Persons in the following categories should be considered for therapy if their tuberculin skin test is positive and they have not previously completed a course of therapy for tuberculosis or LTBI.

I. Persons known or suspected to have HIV infection, regardless of age, including pregnant women.

II. Persons with an abnormal chest radiograph suggestive of tuberculosis and classified as a TB 4, regardless of age.

III. Recent close contacts to active pulmonary or laryngeal TB, regardless of age, including pregnant women.

IV. Tuberculin skin test converters within 2 years, regardless of age, including pregnant women.

V. Persons from countries with high TB rates

A. Recent arrivals (arrived within the past 5 years or less), regardless of age.

B. Remote arrivals (arrived over 5 years ago)

The CDC guidelines no longer recommend using a 35 year-old cutoff in deciding which individuals with LTBI should be treated. In California, where the majority of the TB cases occur in persons born outside of the United States, it is recommended that individuals who arrived over 5 years ago should still receive treatment for LTBI if they have a positive tuberculin skin test. Because the risk of INH-induced hepatitis is greater in older individuals, an age cutoff may be appropriate for this group. Local epidemiologic circumstances and resources should determine whether a specific age cutoff is warranted.

VI. Persons with the following conditions that have been associated with an increased risk of TB (See **Appendix 1, Tables 1 and 2**), regardless of age:

A. Injection drug use, regardless of HIV serostatus

B. Diabetes mellitus (especially insulin-dependent)

C. Silicosis

D. End-stage renal disease

E. Chronic immunosuppression

1. Transplant recipients

2. Prolonged corticosteroid therapy (≥15 mg/day for ≥ 1mo)

3. Other immunosuppressive therapy

F. Hematological and reticuloendothelial diseases

G. Malnutrition and clinical situations associated with rapid weight loss

1. Cancer of the head and neck

2. Intestinal bypass or gastrectomy

3. Chronic malabsorption

4. Low body weight (>10% below ideal body weight)

VII. Children and adolescents < 18 years of age exposed to adults with the above high risk characteristics.

VIII. Residents and employees of the following high risk congregate settings: prison and jails, nursing homes, and other long-term facilities for the elderly, residential facilities for patients with AIDS, and homeless shelters; other homeless persons; employees of hospitals and other health care facilities. In some jurisdictions, local epidemiology and limited resources may necessitate the use of an age cutoff for some populations.

IX. Persons with a positive tuberculin skin test who are not in the above categories.

Local epidemiologic circumstances and resources may define some populations such as persons abusing substances other than injection drugs (e.g. alcoholics and crack cocaine users) or other groups at risk for TB infection for whom treatment is indicated. There may be some of these populations for which an age cutoff is appropriate.

Indications for Treatment of LTBI – TB1 (See **Appendix 2**)

Close Contacts

In close contacts to infectious cases, the initial tuberculin skin test may be negative despite underlying infection with *M. tuberculosis* if the TST is placed before the contact has mounted an immune response to the tuberculin antigen. It takes 2-12 weeks after infection with *M. tuberculosis* to develop a positive TST reaction.

Close contacts (TB1) to an infectious case, who have a tuberculin skin test < 5 mm, should have a chest radiograph obtained, and once TB disease is excluded, should be started on therapy for LTBI regardless of age if (See CDHS/CTCA, "Contact Investigation Guidelines."):

I. Circumstances suggest a high probability of infection. For example, evaluation of other contacts with a similar degree of exposure demonstrates a high prevalence of infection, documented converters, or secondary cases.

II. The contact is a child under 5 years of age, or is infected with HIV, or is otherwise immune-compromised.

For those individuals who are started on therapy with a TST < 5 mm, a repeat tuberculin skin test should be performed 10 to 12 weeks after contact with the infectious case has been broken, or the index case becomes non-infectious, to determine if the skin test has become positive. Decision on continuing therapy should be made once the result of repeat skin testing is available.

Note: In HIV infected contacts, treatment should be completed, regardless of the result of the repeat skin test.

Treatment Regimens

I. INH alone:

A. 6-9 months for immune-competent adults. While a 9-month regimen may provide a greater degree of protection, individual programs may choose to give 6 months of INH due to operational considerations (e.g., resources, adherence issues, etc.)

B. 9 month regimen for children and adolescents (up to age 16 - 18).

C. 9 month regimen for HIV-infected persons or persons suspected of having HIV infection

D. 9 month regimen for TB 4 (See also **below,** IIII)

II. Rifampin alone for 4-6 months. This regimen has not been studied in randomized trials so it should be reserved for those individuals who cannot tolerate INH.

III. INH and RIF for 4 months for TB 4. Although there have been no randomized studies to document the efficacy of this regimen in persons classified as TB 4, there is a great deal of experience with this regimen in the public health sector.

IV. Rifabutin may be substituted for rifampin in the above regimens in situations where rifampin cannot be given such as in HIV-infected persons taking certain protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Dosage adjustments may, however, be necessary. An expert should be consulted.

V. Regimens for Contacts to Drug Resistant Cases

A. Multidrug resistant source case

PZA and EMB, or PZA and a flouroquinolone for 6-12 months for high risk contacts, e.g. immune-compromised persons exposed to MDR-TB cases. These regimens should be given only after TB disease has been ruled out and provided that the organism isolated from the source case is susceptible to PZA, EMB or flouroquinolones. An expert should be consulted.

Daily vs. Intermittent Dosing

INH may be given daily or intermittently. *When given intermittently, INH must be administered as directly observed therapy (DOT), only.*

Directly Observed Therapy

Directly observed therapy (DOT) for LTBI should be used in circumstances where the risk of non-

adherence is judged to be high or when the treatment regimens are given intermittently. New short course regimens and intermittent dosing may make DOT more feasible.

Monitoring for Drug Toxicity and Adherence

I. Baseline Evaluation

A. Baseline laboratory testing is not routinely indicated, even for those over 35 years of age. Such testing may, however, be considered on an individual basis. Persons with the following high-risk characteristics should have baseline laboratory testing:

1. HIV infection
2. History of, or at risk of, chronic liver disease
3. Alcoholism
4. Taking other hepatotoxic medications

Note: Some experts recommend that pregnant women and those in the immediate post-partum period (within 3 months of delivery) have baseline liver function tests measured, also.

B. The baseline laboratory tests will depend on which drug regimen is being used.

1. Isoniazid-containing regimen –If baseline laboratory tests are indicated, a serum AST or ALT and bilirubin should be included.
2. Rifampin (or rifabutin) -containing regimen – In persons taking a rifamycin, baseline measurements of complete blood count and platelets are recommended, in addition to liver function tests.

II. Evaluation During Treatment

A. Clinical Evaluation – Patients being treated for LTBI should receive a clinical evaluation at least monthly, regardless of the regimen used. The evaluation should include careful in person questioning of the patient about side effects associated with the medications, particularly hepatitis (e.g., anorexia, malaise, abdominal pain, fever, nausea, vomiting, dark urine, icterus). In addition, the patient should be asked about adherence and educated about the possible side-effects of the medications.

B. Rifampin regimen requires more frequent monitoring.

C. Routine laboratory monitoring during treatment of LTBI is indicated for those whose baseline liver function tests are abnormal, for persons at high risk of hepatic disease, or persons with symptoms of hepatitis. The frequency of this monitoring will vary depending on the person's risk of liver disease and the severity of the liver function test abnormalities.

Note: Some experts recommend that pregnant women and those in the immediate post-partum period (within 3 months of delivery) have repeat liver function tests measured, also.

Medications should be stopped if the transaminase levels exceed 3-4 times the upper limit of normal if associated with symptoms and 4-5 times the upper limit of normal if the patient is asymptomatic. Medication should be held pending clinical laboratory results.

Note: Any cases of severe liver injury (leading to hospitalization or death) in persons receiving any regimen for LTBI should be reported to the Surveillance and Epidemiology Section of the California Department of Health Services, TB Control Branch at (510) 540-2973, and will be forwarded to the Centers for Disease Control.

Completion of Therapy

Completion of therapy should be based on the total number of doses administered–not on duration of therapy. If treatment is interrupted the recommended number of doses of the regimen should be provided within a certain maximum time period. The entire regimen should be restarted if interruptions were frequent or prolonged enough to preclude completion of doses in the time frames specified. When therapy is restarted after an interruption of more than 2 months, a medical examination to exclude active disease is indicated.

Note: No set of guidelines can cover all individual treatment situations that can and will arise. Thus, when questions on individual situations not covered by these guidelines do arise, consult with the Local TB Control Program, the California Department of Health Services, TB Control Branch, or the Tuberculosis Warmline, for further information.

Suggested Readings

1. American Academy of Pediatrics. 2000. Tuberculosis. *In* Red Book: Report of the Committee on Infectious Diseases, 25th ed. American Academy of Pediatrics, Elk Grove Village IL.

2. American Thoracic Society / Centers for Disease Control and Prevention. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994; 149: 1359-1374.

3. American Thoracic Society / Centers for Disease Control and Prevention. Targeted skin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000 161: S221-S247.

4. American Thoracic Society / Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376-1395.

5. Centers for Disease Control and Prevention. Notice to readers. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2000;49:185-189.

7 Zuber PLF, McKenna MT, Binkin NJ, Onorato IM, Castro KG. Long-term risk of tuberculosis among foreign-born persons in the United States. J.A.M.A. 1997;278:304-307.

Appendix 1

High Risk Populations

Table 1. Incidence of Active TB in Persons with a Positive TST by Selected Factors

Risk Factor	TB Cases/1000 person-years
Infection > 2 years past	**1.6**
Infection < 1 year past	**12.9**
HIV Infection	**35.0-162.0**
Injection Drug Use	
HIV seropositive	**76.0**
HIV seronegative or unknown	**10.0**
Silicosis	**68**
Radiographic findings consistent with old TB	**2.0-13.6**

Source: American Thoracic Society/Centers for Disease Control and Prevention, 2000

Table 2. Certain medical conditions associated with an increased risk of developing TB

Medical Condition	Relative Risk
Solid organ transplant	
Renal	**37**
Cardiac	**20-74**
Jejunoileal bypass	**27-63**
Silicosis	**30**
Chronic Renal Failure/Hemodialysis	**10.0-25.3**
Carcinoma of head and neck	**16**
Gastrectomy	**2-5**
Diabetes mellitus	**2.0-4.1**

Source: American Thoracic Society/Centers for Disease Control and Prevention, 2000

Appendix 2

CANDIDATES FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) (adapted from Charles P. Felton National TB Center)			
Category of person tested	TST <5 mm	TST ≥5 mm	TST ≥10 mm
(A) Recent Contact to TB Case [1]			
1. Child <5 years and recent contact[2]	TREAT	TREAT	TREAT
2. HIV-infected and recent contact[2]	TREAT	TREAT	TREAT
3. Immunosuppressed and recent contact[2]	TREAT	TREAT	TREAT
4. Other recent contact of TB case	Do Not Treat	TREAT	TREAT
(B) No Recent Contact to TB Case			
1. Fibrotic changes on chest X-ray[3]	Do Not Treat	TREAT	TREAT
2. HIV-infected	Do Not Treat	TREAT	TREAT
3. Injection drug user with unknown HIV status	Do Not Treat	TREAT	TREAT
4. Other immunosuppressed persons[4]	Do Not Treat	TREAT	TREAT
5. Recent skin test converters within 2 years	Do not Treat	Do Not Treat	TREAT
6. Foreign-born persons from endemic country[5]	Do Not Treat	Do Not Treat	TREAT
7. Injection drug user known to be HIV negative	Do Not Treat	Do Not Treat	TREAT
8. Resident/Employee institutional setting[6]	Do Not Treat	Do Not Treat	TREAT
9. Mycobacteria lab personnel	Do Not Treat	Do Not Treat	TREAT
10. High-Risk clinical conditions[7]	Do Not Treat	Do Not Treat	TREAT
11. Children < 18 years of age exposed to adults at high risk	Do Not Treat	Do Not Treat	TREAT
12. Other persons depending on local epidemiology and resources	Do Not Treat	Do Not Treat	TREAT

Note: If a person meets more than one criteria for treatment, the lower TST cut point for therapy should be used (i.e. an immigrant from a TB endemic country who has fibrotic changes on chest radiograph should be treated if the TST is ≥ 5 mm

[1]Recent contacts to active case of pulmonary or laryngeal TB.

[2]Recent contacts who are initially TST-negative should have a TST repeated 8-12 weeks after last exposure to TB case (see Text). Treatment can usually be discontinued after negative second TST in children. HIV infected adults and children, however, should receive full course of therapy regardless of TST result.

[3]Abnormal, stable, radiographic findings (parenchymal abnormalities consistent with TB, not isolated calcified granuloma or apical pleural thickening). Bacteriologic studies should be obtained for all persons with an abnormal chest radiograph consistent with TB even when the radiographic abnormalities appear stable. When bacteriologic studies are obtained, treatment of LTBI should not be initiated until final culture results are available.

[4]Transplant recipients, prolonged corticosteroid therapy (≥15 mg/day for ≥1 month), other immunosuppressive therapy

[5]Local epidemiologic circumstances and resources should determine whether a specific age cutoff is warranted in persons who have resided in the U.S. for over 5 years.

[6]Residents and employees of the following high risk congregate settings: prisons and jails*, nursing homes and other long-term facilities for the elderly, residential facilities for patients with AIDS, homeless shelters; other homeless persons; employees of hospitals and health care facilities.

*The California Department of Corrections considers all inmates high risk, and therefore treats for latent infection all inmates ≥ 5mm.

[7]Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas), other specific malignancies (e.g. carcinoma of the head and neck or lung), weight loss of ≥ 10% of ideal body weight, gastrectomy, jejunoileal bypass.

Pregnancy: Treat during pregnancy if either HIV-infected or recent *M.tb* infection.